Fast microwave-assisted oxidation of 1,4-dihydropyridines with $FeCl_3.SiO_2$

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Pyridine derivatives are easily obtained in high yields by microwave-promoted rapid oxidation of the corresponding 1,4-dihydropyridines with ferric chloride hexahydrate and silica gel under solvent-free conditions.

Keywords: 1,4-dihydropyridines, ferric chloride, microwave, oxidation

The oxidation of Hantzsch 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines has attracted considerable attention since they have been extensively utilised as the analogues of NAD(P)H coenzymes to study the mechanism and synthetic potential of various redox processes.[1] In addition, some 1,4-DHP based antihypertensive drugs (Ca^{2+} channel blockers) have been used in the treatment of various cardiovascular disorders.[2] Consequently, this aromatisation reaction continues to attract the attention of researchers seeking milder and general protocols applicable to a wide range of 1,4-dihydropyridines. Many of the reported reagents involve the use of oxidants including CrO_3,[3a] HNO_3,[3b] $KMnO_4$,[3c] DDQ,[3d] $Bi(NO_3)_3$,[3e] $FeCl_3.6H_2O$,[3f] PCC,[3g] CAN,[3h] Bentonite clay supported manganese dioxide,[3i] NO,[3j] $RuCl_3/O_2$,[3k] $Mn(OAC)_3$.[3l]

However, some methods suffer from low chemical yields, strong oxidative conditions, cumbersome workup procedures or side product formation. Therefore, it is still necessary to find a milder and high yielding oxidant for the Hantzsch 1,4-DHPs.

The use of inorganic supports as reaction media has received increasing attention in recent years because of the improved efficiency of many surface bound reagents.[4] Furthermore, with the advent of microwave (MW) dielectric heating, the rates of organic reactions can be accelerated to afford faster and cleaner chemical conversions. [5] However, many existing procedures are subject to the limitation that the preparation of supported reagents can require longer reaction times, tedious procedures or prolonged activation under special conditions such as reduced pressure.[6]

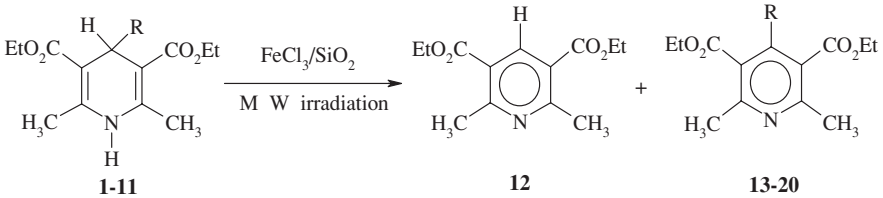
In continuation of our ongoing program to develop environmentally benign solvent-free methods,[7] we considered the convenient solventless oxidation of 1,4-DHPs and noted that metallic salts impregnated on silica gel have been utilised in a variety of methods for organic oxidations.[8] However, the preparation of the required reagents raises the problems noted previously. Among those reagents for the transformation of Hantzsch esters into pyridines, $FeCl_3.SiO_2$ has not been used. We hereby report the preparation of a silica gel and ferric chloride (silferc) reagent by co-grinding $FeCl_3.6H_2O$ and chromatographic silica gel (230–400 mesh) in an agate mortar.(Scheme) Although $FeCl_3.SiO_2$ is an air-stable reagent care was taken to minimise exposure to air due to the potential hygroscopicity of this reagent. The reactions were performed in a commercially available household microwave oven in a small beaker.

The 1,4-DHPs **1**–**11** were reacted with 2 equivalents of $FeCl_3.SiO_2$. All the 1,4-DHPs were consumed after 2 minutes, with the exception of 4-aryl DHPs bearing electron-withdrawing groups (entries **7** and **8**) that required a somewhat longer reaction time, 3 min, for complete conversion. Inspection of the Table reveals that $FeCl_3.SiO_2$ is an efficient reagent and the reaction times have been reduced compared to the conventional method.

Complete dealkylation occurs when the 1,4-DHPs bear a secondary alkyl group or a benzyl group at the 4-position. We observed (Table) that reaction times are dependent slightly on the nature of the substituent at the 4-position in the starting 1,4-DHPs. After chromatography or crystallisation the corresponding pyridines were isolated in good yields. Corresponding reaction times and yields from thermal heating techniques have been included in Table 1 for comparison. A further advantage of this dry medium technique is that no subsequent neutralisation is required as would be the case in many reactions which employ acetic acid as solvent.

Longer microwave irradiation times were found to increase the formation of side products. Whilst oxidation of 4-MeDHP **2** gave only the pyridine derivative **13**, the reaction with 4-isoPrDHP **3** produced a mixture of **12** and **14**. This is attributed to increased electron releasing ability and consequent greater stability of the corresponding secondary alkyl cation.

In conclusion, the use of $FeCl_3.SiO_2$ reagent for the microwave-assisted oxidation of DHPs provides a technique which is very fast, simple and ecofriendly.



1-11 **12** **13-20**

Scheme 1

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Table 1 Microwave-promoted oxidation reaction of 1, 4-DHPs[a, b]

Entry	R	Time MW/min	Product	Isolated yield/%	M.p. /°C	Lit. m.p. °C	Thermal heating[3f]	
							Time /min	Isolated yield /%
1	H	1	12	95	69–70	69–70[3d]	60	60
2	CH_3	2	13	90	liq	liq [3e]	–	–
3	$CH_3CH_2CH_2$[c]	2	14	75	liq	liq [3d]	60	62
4	$(CH_3)_2CH$	2	12	85	69–70	69–70[3d]	60	72
5	C_6H_5	2	15	93	62–63	63–64[9]	60	57
6	$C_6H_5CH_2$	2	12	82	69–70	69–70[3d]	–	–
7	4-ClC_6H_4	3	16	85	66–67	65–67[3d]	60	77
8	3-$NO_2C_6H_4$	3	17	80	61–63	61–63[3d]	60	62
9	4-$CH_3OC_6H_4$	2	18	90	50–52	51–53[3l]	60	68
10	4-$CH_3C_6H_4$	2	19	91	71–72	72–73[3l]	–	–
11	2-Furyl	2	20	88	liq	liq[3l]	60	74

[a]All of 1, 4-DHPs were prepared according to literature procedure.[9]
[b]All products are known compounds and were characterised by their mps and NMR spectra.
[c]Compound 12 was also detected.

Experimental

In a typical experimental procedure, $FeCl_3.6H_2O$ (0.27 g, 1 mmol) was mixed with silica gel (0.54g). The 1,4-dihydropyridine (0.5mmol) was added to the above supported reagent and mixed thoroughly in an agate mortar. The reaction mixture was transferred to a beaker which was placed in a domestic microwave oven and irradiated for the required period of time to complete the reaction (as monitored by TLC). The reaction mixture was extracted with chloroform, the filtrate evaporated and the residue crystallised from aq. EtOH to afford the corresponding pyridine, (see Table).

Received 1 August 2004; accepted 22 November 2004
Paper 04/2693

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